300-120

GP1801

PATENT
Docket No. 220002016004
Client Ref. UC-80-065-4

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6-16-97
Date

Alexandra H. Parsons
Alexandra H. Parsons

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the application of:

Walter L. MILLER et al.

Serial No.: 08/487,312

Filing Date: 7 June 1995

For: BOVINE GROWTH HORMONE

Examiner: C. Saoud

Group Art Unit: 1801

BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants appeal the rejection of claims 19-22. Final rejection was mailed 16 October 1996; a Response was filed 16 January 1997 along with a Notice of Appeal. A Petition for an Extension of Time to file this Brief of three months until 16 June 1997 is attached along with the required fee. Reversal of the rejection is requested. In accordance with 37 C.F.R. § 1.192, this Brief, along with the Appendix, is filed in triplicate and is accompanied by the required fee.

I. Real Party in Interest

The present application is assigned to the Regents of the University of California.

II. Related Appeals and Interferences

Applicants are unaware of any related appeals or interferences which would have a bearing on the Board's decision.

III. Status of Claims

This application was filed as a continuing application of a specification to which 16 claims were appended. The application was filed along with a preliminary amendment which canceled claims 2-16 and added claims 17-19. In response to a restriction requirement, applicants elected to prosecute the invention of claim 19. In response to an initial rejection, claims 20-22 were added, and claim 19 was amended to place it in independent form. The Examiner withdrew claims 1 and 17-18 from consideration. Thus, claims 1 and 17-18 are withdrawn from consideration and claims 19-22 are pending and are on appeal.

IV. Status of Amendments

No amendments to the claims were proposed subsequent to final rejection.

V. Summary of Invention

The invention is directed to bovine growth hormone produced recombinantly. The parent application herein, Serial No. 07/480,745 filed 15 February 1990 claims the recombinant materials themselves and a method for producing the claimed hormone. Claims directed to these recombinant aspects have been allowed in the parent. The present claims are directed to the protein product itself. The application describes the production of this claimed protein beginning on page 6, line 2 and continuing to page 10, line 17. Production in bacteria is exemplified beginning on page 17, about line 20 to page 18, third-to-last line. The recombinantly produced bovine growth hormone comprises the amino acid sequence at positions 2-191 of Figure 1 in the

present application or an allelic variant. It is described as useful to stimulate the growth of bovine subjects (Pages 1-2, bridging paragraph).

VI. Issues

There is only one issue in this case: whether the claimed protein is anticipated by, or made obvious by, the purified bovine growth protein prepared from pituitaries by Daniels *et al.*, U.S. Patent No. 3,265,579.

VII. Grouping of Claims

The claims may be considered together.

VIII. Argument

Appellant does not dispute that the claims at issue are product-by-process claims, and further does not dispute that the patentability of the subject matter resides in the patentability of the product, not the patentability of the process. However, the process itself confers certain properties on the product that would not be present were the process claimed not used. These conferred properties are properly considered in determining patentability. Briefly, in the present case, the required process confers on the claimed product the assurance that it is free of whatever might be the infectious agent in "Mad Cow Disease." Prior art compositions may be free of this disease-causing agent, but they cannot offer any assurance of this freedom and are thus essentially useless with respect to the disclosed use of the hormone.

If the Process Limitations *per se* are Reflected in a Mandated Characteristic of the Claimed Product, the Process Limitations will be Read into the Claim

This precise issue was faced by the CCPA in *In re Wakefield and Foster*, 164 USPQ 636 (CCPA 1970). The claims in *Wakefield* were quite analogous to those herein. They were

directed to a "synthetic" rubber. The word "synthetic" was read as a process limitation into the claim which had an impact on the nature of the product *per se*. The court concluded that the appellants had

> excluded from the scope of their claims any purified natural product by the recitation "synthetic." This word, as we have shown above, has a reasonably precise meaning and therefore does not render the claims indefinite.

The Board went on to state that the word alone did not make the product new, but, at page 641, rejected the Examiner's view that the synthetic product is so similar to the natural product purified to the extent allegedly shown in the prior art as to be *prima facie* obvious. The court went on to hold that any tentative conclusion of obviousness would be rebutted where, at the time the invention was made, no known or obvious method of making the claimed composition existed. As has been pointed out above, claims to the method for obtaining recombinant bovine growth hormone have been allowed in the parent application, thus the method was not known.

Nevertheless, appellants do not rely on the patentability of their process for patentability of the claimed product. It is the characteristics conferred upon the claimed product by virtue of the process limitations that thus confer patentability.

The Bovine Growth Hormone of the Daniels Reference Differs from the Bovine Growth Hormone Claimed

The bovine growth hormone purified from pituitaries by the cited reference may or may not be homogeneous and may or may or may not be free of the causative agent for bovine spongiform encephalopathy (BSE) commonly known as Mad Cow Disease. Appellants agree that it is quite unlikely that the actual material exemplified in the Daniels patent contained this agent. However, there is absolutely no guarantee that the Daniels preparation is free of this agent, while the process parameters of the present claims assure that the claimed protein will be thus characterized.

There is a plethora of evidence of record that such absolute assurance is required to make any preparation of bovine growth hormone useful. The issue is far from dead. Enclosed herewith is an additional report, dated 4 June 1997 from the *Washington Post* describing new FDA regulations to prevent Mad Cow Disease in the U.S. These precautions are taken even though Mad Cow Disease has not been shown to be a problem here. In essence, the FDA is prohibiting the use of animal proteins in feed to prevent any possible transmission of the disease, regardless of the fact that it has not so far been detected. This again illustrates, as has the complete record herein, that the assurance of safety is a real property of a material aside from the physical make-up of any particular sample.

It has already been shown in the record below that the very remote possibility that human growth hormone obtained from pituitaries might contain a comparable disease-causing agent responsible for Creutzfeldt-Jakob's Disease (CJD) was sufficient to remove the "native" product from the market and substitute for it the recombinant form. Similarly, here, it seems clear that it will never be possible to use bGH purified from bovine pituitaries to enhance milk production or stimulate growth in cattle; rather, the recombinant form will clearly be required.

The Interpretation of Product-by-Process Claims in Regard to Infringement is Related to the Nature of the Claim

The Examiner implies that as the claims are to be examined for the novelty and nonobviousness of the product, the process limitations will not be read into the claims, and thus their scope could be considered to read on bovine growth hormone that was prepared by other than a recombinant process. The only case that we have found which would support such a position is the Federal Circuit panel decision in *Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 1576, 18 USPQ2d 1010 (Fed. Cir. 1991) at 1016 which holds that claims to Factor VIII prepared by a particular purification process would be infringed by recombinantly produced Factor VIII, as the claims are putatively directed to the product not the

process. In this case, *there was no contention that the nature of the process influenced the nature of the product.* Hence, this holding is not applicable to the present set of facts.

This situation is further complicated by the holding of a different panel in *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 5 F.3d 1477, 1480, 28 USPQ2d 1343, 1346 (Fed. Cir. 1993), and 970 F.2d 834, 836, 837, 846, 23 USPQ2d 1481, 1483, 1491 (Fed. Cir. 1992) where plastic athletic shoe soles, putatively the same as those made by the disclosed process, but made by a different process, were held not to infringe a product by process claim.The *Atlantic Thermoplastics* court cited several lines of cases from the Supreme Court and from the CCPA holding that process limitations cannot be ignored when evaluating infringement of a claim. This discussion is incorporated herein by reference. An attempt to rehear this case *en banc* was denied by the Federal Circuit.

Appellants believe that in the present case, where the product is distinguished from the prior art by virtue of the process itself, in that the process leads to a product that is different from what appears to be a similar product prepared by a different process, there would be no doubt that the process limitations would be read into the claims to evaluate infringement. To do otherwise would clearly make no sense.

The Arguments Made by the Examiner Assume that a Structural Difference between the Prior Art Compositions and the Claimed Protein is Required

The compositions of Daniels are unlikely to be structurally identical to the compositions of the present claims, but appellants have not adduced experimental evidence to demonstrate this. This is because the process-conferred distinction is not so literal as that. If this literal distinction were relied upon, the argument of the Examiner that the "virus" that causes BSE does not copurify with bGH and that the preparation of Daniels, presumably from North American cows, is probably free of the agent anyway, might be relevant. In this event, appellants point out that it is not clear that BSE is, indeed, caused by a virus and the nature of the causative agent is not

known. See the enclosed article, "Mice Inoculated with Infectious 'Mad Cow' Brain Tissue Belie Accepted Prion Wisdom," *BioWorld Today*, January 17, 1997, page 1. It is clear from this article that the nature of the causative agent is still unknown and that any statements made in 1985, such as those cited by the Examiner on page 4 of the final rejection, cannot be taken at face value. Nevertheless, even assuming that the Daniels preparation as made is, in fact, free of the BSE causative agent, the important distinction is that it cannot be guaranteed to be so. It is this guarantee that makes for the patentable distinction.

Conclusion

The claimed bovine growth hormone protein prepared by recombinant means has the inherent property, conferred by the process by which it is made, of a warranty of freedom from the causative agent for BSE. This advantage is inherent in the description in the specification wherein the use of the claimed product is to stimulate the growth of cattle (see pages 1-2, bridging paragraph). The fact that this advantage exists does not need to be set forth *in haec verba* in the specification. *In re Chu*, 36 USPQ2d 1089 (Fed. Cir. 1995). Thus, the process limitations in the claim are meaningful and result in a patentably distinct product independent of the patentability of the process. The characteristic of providing an actually useful product in that it can be guaranteed free of the causative agent for BSE is accomplished by virtue of carrying out the described process.

The arguments made in response to final rejection in the Response filed 16 January 1997 are incorporated herein by reference.

IX. Appendix

Attached hereto is a copy of the claims on appeal.

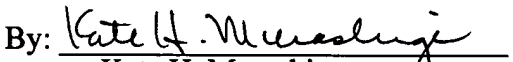
Summary

Withdrawal of the rejections and issuance of claims 19-22 is respectfully requested.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to Deposit Account No. 03-1952.

Dated: June 16, 1997

Respectfully submitted,

By: 

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Attached: Appendix A
(copy of claims involved in the Appeal)

THE FEDERAL PAGE

FDA Moves Against 'Mad Cow' Disease

Rules Will Prohibit Use of Protein From Most Mammals in Veterinary Feeds

By John Schwartz
Washington Post Staff Writer

The Food and Drug Administration announced rules yesterday intended to prevent outbreaks of "mad cow" disease in American cattle herds.

The agency will prohibit the use of protein derived from most mammals in veterinary feeds given to ruminant animals such as cows, sheep and goats, though pig proteins will still be allowed. The rule will take effect in two months.

No cases of bovine spongiform encephalopathy (BSE), the scientific name for mad cow disease, have ever been detected in U.S. herds. But the disease caused a food panic in England last year as more than 100,000 cattle were found to be infected and had to be destroyed. The disease spread as the bodies of infected cows and sheep infected with a similar disease, scrapie, were rendered and used in feeds given to other cattle.

At least 16 cases of a similar ailment in humans, known as new variant Creutzfeldt-Jakob disease, have been linked to eating infected British beef.

The new FDA rules are an attempt to prevent a similar tragedy from occurring in the United States. No case of bovine spongiform encephalopathy has ever been documented in this country, but "if a case of BSE were ever found here, these measures would prevent the spread of BSE through feeds," the FDA said in a statement yesterday.

This final version of the FDA rule is somewhat tougher than the initial proposal by the agency in January. That version would have prohibited the use of meat from ruminants in ruminant feed. Swine and poultry proteins will still be allowed in ruminant feed because FDA researchers were unable to confirm any instances of mad cow-like diseases occurring under natural conditions in those animals, said Stephen F. Sundlof, director of the agency's Center for Veterinary Medicine. Feed derived from mammals can still be given to pigs and poultry under the new rule, and can also be used in pet foods.

The tougher protein standards are a nod to practicality, FDA officials said. Many of the nation's 300 rendering plants process meat from a number of different species, so it would be difficult if not impossible to enforce restrictions on one kind of meat vs. another. A number of plants, however, deal exclusively with swine, and so the agency believed that a rule allowing protein from those plants would not inadvertently bring meat from other animals into the feed supply.

The new rule also will continue to allow the use of products that are "believed to pose a minimal risk of BSE transmission," the agency said, including blood, gelatin, milk and milk products, as well as horse meat.

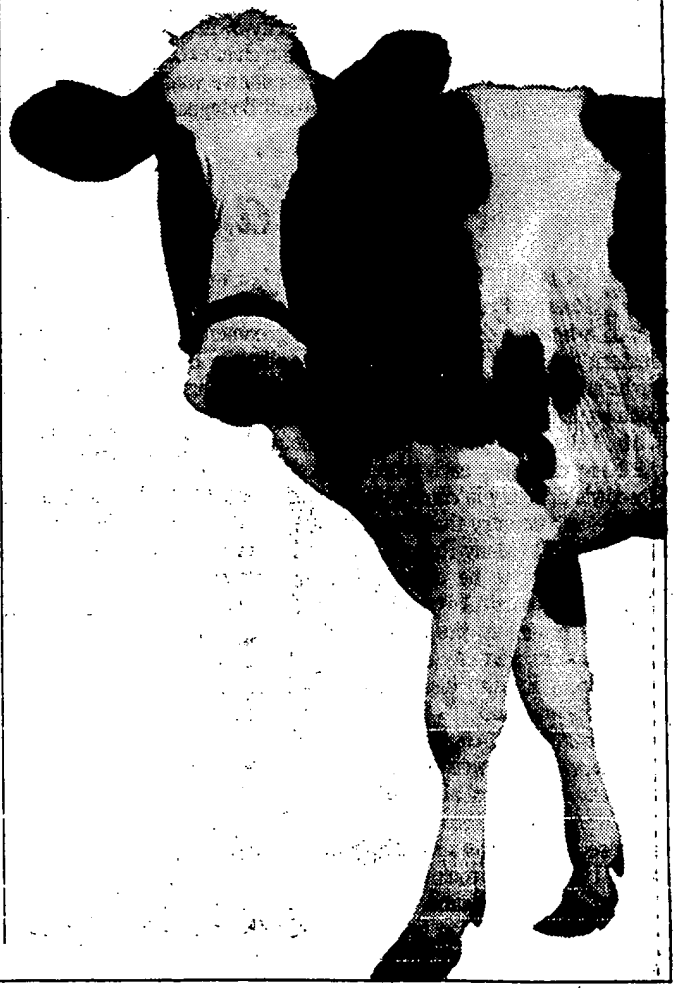
One consumer group said the exception for pigs was a fatal flaw in the new rule. Consumers Union cited a British experiment in which one of 10 pigs injected with brains from infected cows became infected with the disease. "FDA has left the door open for a mad cow-like disease to circulate in the United States," said Michael Hansen, a food safety researcher with the group, in a statement.

But Sundlof countered that each pig received an injection of the infectious material in the abdomen, intravenously and directly into their brains, bypassing whatever protective mechanisms may exist in the digestive system, making transmission of the disease much easier. "They used some pretty drastic measures in order to cause the disease," Sundlof said. "We'd like to see one natural case before we condemn a whole industry."

Another food safety group applauded the new FDA rule. By instituting the feed ban, the U.S. government is "clearly moving in the right direction," said Caroline Smith DeWaal, director of food safety for the Center for Science in the Public Interest. "We've taken the first important step to prevent mad cow disease from reaching epidemic proportions in U.S. cattle. The question now is whether additional steps are needed to prevent it from becoming an issue in the human food supply."

A representative of the rendering industry said it would comply with the new regulations. Don Franco, director of scientific services for the Alexandria-based National Renderers Association, said that his group believed that the science linking animal-derived feeds produced under current American standards to diseases such as mad cow was still unsettled, but that the group would go along with the ban.

"We thought, hey, if that's what the government wants," Franco said, "how do you fight that? How do you fight prevention?"



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BIOWORLD® TODAY

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THE DAILY BIOTECHNOLOGY NEWSPAPER

VOLUME 8, NO. 11
PAGE 1 OF 4

GenPharm Files Patent Suit

Cell Genesys Drops Trade Secret Case Against GenPharm

By Charles Craig
Staff Writer

Cell Genesys Inc. has dropped its three-year-old California lawsuit accusing GenPharm International Inc. of stealing trade secrets related to development of transgenic mice for production of human antibodies to treat diseases.

However, the legal fight between the two firms over intellectual property rights to the technology continues on other fronts.

GenPharm, of Palo Alto, Calif., has filed two patent infringement lawsuits in U.S. District Court in San Francisco against Cell Genesys, of Foster City, Calif. Another battle also could be brewing at the U.S. Patent and Trademark Office in Washington.

GenPharm officials said Cell Genesys' dismissal of the state court case two weeks before the trial was to start proves the allegations of trade secret theft were false.

Cell Genesys officials, however, told *BioWorld Today*

See Cell Genesys, Page 2

ICOS, Suntory Form $30M Joint Venture To Develop Inflammatory Disease Drug

By Charles Craig
Staff Writer

Suntory Ltd. and Icos Corp. formed a $30 million joint venture company, called Suncos Corp., to develop recombinant platelet-activating factor acetylhydrolase (PAF-AH) as a treatment for inflammatory disorders, such as asthma and acute respiratory distress syndrome (ARDS).

Suntory, of Tokyo, is contributing $30 million in cash to launch Suncos while Icos, of Seattle, is supplying the potential drug, PAF-AH, which was valued at $30 million. The companies will share equally in future expenses.

Lacy Fitzpatrick, Icos' manager of investor relations, said PAF-AH is a naturally occurring enzyme that breaks down platelet-activating factor (PAF), whose overproduction is associated with inflammatory diseases.

Suncos initially will target ARDS, asthma and acute pancreatitis with the PAF antagonist. A Phase I trial in 1996

See Icos, Page 3

Can 'Mad Cow' Disease Infect Humans?

British Statistician Predicts Future Creutzfeldt-Jakob Disease Epidemic Is Unpredictable

By David N. Leff
Science Editor

Whom the Gods would destroy, they first make mad.

Brought up-to date, this famous line by Longfellow might read today: "Whom the Gods would destroy — man or beast — they first send prions."

Prion infection — 'mad cow' disease — today is decimating several million cattle in British herds. (See *BioWorld Today*, Dec. 20 and April 8, 1996, p. 1.)

This bovine spongiform encephalopathy (BSE) may also have infected 14 young men and women in the U.K. with the human equivalent of BSE, Creutzfeldt-Jakob disease (CJD). In 13 of the 14, clinical onset occurred during 1994 or 1995; BSE surfaced in 1988 — a likely incubation interval for the human infection (see related article on this page).

See Mad Cow, Page 4

Mice Inoculated With Infectious 'Mad Cow' Brain Tissue Belie Accepted Prion Wisdom

By David N. Leff
Science Editor

Ask a prion disease researcher how the infectious particle infects its host victim. The answer will likely be:

A normal prion protein, PrP, turns pathogenic by changes in its basic molecular shape. This abnormal, malformed switch from Jekyll to Hyde is protease-resistant, so the particle acquired the designation, PrPres. It replicates by inducing is recipient organism to take on the abnormal prion conformation.

See Prion, Page 3

Publication Notice

BioWorld Today's offices will be closed on Monday in honor of Martin Luther King's Birthday. Our offices will reopen on Tuesday, Jan. 21.

INSIDE: OTHER NEWS TO NOTE

OTHER NEWS TO NOTE

• **LXR Biotechnology Inc.**, of Richmond, Calif., raised $2.8 million in a final phase of a private placement of stock at $2 per share. The placement generated a total of $10.4 million in gross proceeds.

• **Matrix Pharmaceutical Inc.**, of Fremont, Calif., began selling Accusite injectable Gel in the U.K. for external genital warts. In late December 1996, the company received a non-approvable letter from the FDA for the product in the U.S. Matrix said it will meet with the FDA to discuss questions raised in the new drug application. Accusite is a biodegradable gel containing fluorouracil, a chemotherapeutic agent.

• **Neoprobe Corp.**, of Dublin, Ohio, received approval in South Korea for RIGScan CR49, a radioactive monoclonal antibody, designed to assist surgeons in detecting cancer sites. The product will be marketed in South Korea for metastatic colorectal cancer.

• **Oxis International Inc.**, of Portland, Ore., filed an investigational new drug application with the FDA to begin clinical trials of an oral form of BXT-51072, which is targeted for treatment of inflammatory bowel disease. The drug is a molecule that mimics the natural antioxidant enzyme, glutathione peroxidase, which controls levels in cells of potentially damaging free radicals and reactive oxygen species.

• **Paracelsian Inc.**, of Ithaca, N.Y., entered a cooperative research and development Agreement (CRADA) with the National Institutes of Health, of Bethesda, Md. The CRADA extends work being done by Paracelsian and the NIH's National Cancer Institute on screening extracts from traditional Chinese medicinal herbs for compounds that modulate cell signaling pathways involved in HIV and cancer.

• **SciClone Pharmaceuticals Inc.**, of San Mateo, Calif., received FDA approval to begin clinical trials of its cystic fibrosis treatment, CPX, which was licensed from the National Institutes of Health in Bethesda, Md. The drug, 8-cyclopentyl-1, 3-dipropylxanthine, is designed to correct improper transport of sodium and chloride across epithelial cells, which is the source of the lung disease.

• **TheraTech Inc.**, of Salt Lake City, entered a collaboration with **Eli Lilly and Co.**, of Indianapolis, for development of peptides using TheraTech's oral transmucosal delivery system. Financial terms were not disclosed.

• **Tularik Inc.**, of South San Francisco, extended its collaboration with **Merck & Co.**, of Whitehouse Station, N.J., on development of antiviral drugs against HIV and hepatitis C. The companies said their partnership was extended another three years. Financial terms were not disclosed.

Cell Genesys

Continued from Page 1

the same intellectual property claims at issue in the state court case will be argued in the federal court patent infringement litigation. In addition, they noted, the trade secret lawsuit could be revived in California court.

In February 1994, Cell Genesys filed a lawsuit alleging a scientific consultant to the company gave GenPharm technology for creating transgenic mice to produce human monoclonal antibodies. (See *BioWorld Today*, Feb. 2, 1994, p. 1.)

GenPharm denied the allegations and accused Cell Genesys of filing the court suit in retaliation for losing the race to develop transgenic mice. (See *BioWorld Today*, Feb. 3, 1994, p.1.)

GenPharm CEO Jonathan MacQuitty said Thursday the Cell Genesys trade secret lawsuit forced his company to cancel plans for an initial public offering in 1994. He noted GenPharm remains privately held and he blamed uncertainty caused by the litigation for his firm's difficulty in negotiating partnerships and in raising funds.

With Cell Genesys' withdrawal of the state court case, GenPharm will accelerate development of monoclonal antibodies, he added.

MacQuitty said the company has several antibodies in preclinical studies and expects to begin clinical trials with one of them within 12 months.

Cell Genesys has formed a subsidiary company, Abgenix Inc., to conduct antibody development. Kathleen Glaub, Cell Genesys' chief financial officer, said clinical trials will begin this year with a monoclonal antibody against interleukin-8 for treatment of inflammatory disorders.

GenPharm's federal court lawsuits involve patents issued to the company in 1996 and in January 1997 for development of transgenic mice and their use to produce human antibodies. The first patent infringement action was filed in October 1996 against Cell Genesys and the second suit was filed last week. ■

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OTHER NEWS TO NOTE

• **Vertex Pharmaceuticals Inc.**, of Cambridge, Mass., said its partner, **Glaxo Wellcome plc**, of London, began a Phase II trial of the former's HIV protease inhibitor, VX-478, in combination with other protease inhibitors. Three groups of patients in the open-label study will receive the Vertex drug together with Invirase (saquinavir), Crixivan (indinavir) or Viracept (nelfinavir), which are made by **Roche Holding Ltd.**, of Basel, Switzerland, **Merck & Co.**, of Whitehouse Station, N.J., and **Agouron Pharmaceuticals Inc.**, of La Jolla, Calif., respectively. A fourth group will take VX-478 with Glaxo Wellcome's two reverse transcriptase inhibitors, Retrovir (AZT) and Epivir (3TC).

Icos

Continued from Page 1

showed the treatment was safe. Several Phase II trials are planned this year.

Fitzpatrick said the Icos-Suntory collaboration was modeled after Amgen Inc.'s successful joint venture with Kirin Brewery Co. Ltd., of Tokyo. Amgen and Kirin teamed up in 1984 to develop erythropoietin (Epogen) and expanded their joint venture in 1986 to include another potential protein drug, granulocyte-stimulating factor (Neupogen).

Epogen, a red blood cell booster, and Neupogen, a white blood cell booster, are Amgen's only marketed products, generating $2 billion in annual sales for the Thousand Oaks, Calif., company.

Fitzpatrick said Icos favored a joint venture over a product licensing deal because "it's been found you get much more of a commitment from your partner. You get management commitment and financial commitment."

Suntory will market the product in Japan and Icos will sell it in the U.S. Suncos, which will receive royalties from sales in those two regions, retained rights to the drug in Europe and elsewhere.

Suntory's interest in PAF-AH, Fitzpatrick said, stemmed from the company's own research on the enzyme.

Icos' stock (NASDAQ:ICOS) closed Thursday at $8.312, unchanged from the day before. ■

Correction

An Other News To Note item in *BioWorld Today* Jan. 16, 1997, on Boston Life Sciences Inc., of Boston, should have identified Altropane as a radio-imaging agent for diagnosis of Parkinson's disease.

Prion

Continued from Page 1

As such, it's the infectious agent in all of the transmissible spongiform encephalopathies (TSE), from the bovine form, BSE, to the predominant human equivalent, Creutzfeldt-Jakob disease. (see related article on p. 1.)

That scenario defines the prevailing "prion hypothesis."

French findings, reported in today's issue of *Science*, dated Jan. 16, 1997, challenge that doctrine. The paper's suggestive title: "Transmission of the BSE agent to mice in the absence of detectable abnormal prion protein."

Neurovirologist and veterinary surgeon Corinne Lasmezas is the paper's first author.

"What we saw in our experiments," she told *BioWorld Today*, "was that the abnormal prion agent may be able to replicate in its recipient animal without inducing accumulation of the prion protein's abnormal form."

She and her co-authors at the French Atomic Energy Commission's Neurology Branch, in Fontenay-aux-Roses, injected a homogenate of brain tissues from British BSE cattle directly into the brains of 30 mice.

Within 368 to 719 days, all of the inoculated animals had symptoms of a neurological disease—hind limb paralysis, tremors, hypersensitivity to stimulation, apathy, hunched posture. And their brains revealed neuronal death.

Yet, the brain tissue in 55 percent of those 30 mice showed no signs of PrPres, the designated hitter of prion infectivity. They were devoid of spongiform vacuolation, the hallmark of TSE. Nevertheless, they were able to transmit the infection.

A second set of mice got cerebral inoculation with brain material from both the PrPres-positive and negative cohorts among the initial 30. Most of them developed the classical disease, but with markedly shorter incubation periods.

A third passage reduced incubation times still further, and all but eliminated the animals lacking the infectious PrPres protein.

Thus, said Lasmezas, putting a new twist on the prion doctrine, "PrPres is clearly involved in the pathogenic process of TSEs. However, it may not be the transmissible component of the infectious agent."

Her group is now "investigating the role of the normal prion protein. Is it, for example, a receptor of the agent? Or what is its role?"

She concluded: ""If we can infect PrP normal mice with the nucleic-acid-like agent we have identified in our work, it would mean that the role of PrP is not what has been taught until now. But that's just getting under way in our lab." ■

Mad Cow

Continued from Page 1

But the transmission of BSE to CJD, though likely, is still speculative.

Twelve of the 14 have already died of this invariably fatal infection; the other two have not long to live.

But BSE has driven thousands, if not millions, of other British subjects mad with worry. They fear that those 14 victims acquired their death sentences by transmission from the infected cattle, and that they are merely the tip of an enormous CJD epidemic to come.

At a news conference in London on Wednesday, Jan. 15, medical statistician Simon Cousens, of the London School of Hygiene and Tropical Medicine, presented data to the press that addressed these public anxieties.

Cousens' appearance before the media coincided with publication of those data in the latest issue of *Nature*, dated the same day, Jan. 15, 1996. His paper's title: "Predicting the CJD epidemic in humans."

It's based on the probable but unproven premise that the new clinical variant of CJD arises from exposure to the infectious prion agent that causes BSE.

"So few cases, only 14, over a reasonably long period of extended time," Cousens told the gathered journalists, "helped us to rule out the more catastrophic scenarios that were causing such public concern."

After summarizing the "dense" statistical-mathematical epidemiological estimates in his *Nature* article, Cousens addressed the question: "Having observed at this point in time a very small number of cases, can we say that there will not be a lot of cases in the future?

"The clear answer coming out of our statistical models," he answered, "is no, we can't say now."

Explaining this bottomless bottom line, Cousens pointed out: "There's an enormous range of possibilities, from hundreds to thousands of new cases, compatible with our observations so far."

Those observations extrapolate from the 14 individuals stricken to date, backward in time to the emergence of 'mad cow' disease in 1988, and forward in time to an array of alternative predictions, based on a spectrum of highly uncertain but plausible assumptions.

"If we were to continue observing a small number of cases each year," Cousens told *BioWorld Today*, "and there were evidence of a sharp increase in CJD incidence, we might predict 25 to 50 to 100 cases over several years ahead.

"On the other hand," he added, "if we see a sharp acceleration over the next few years, we're looking at the possibility of thousands and thousands of cases."

Between those two extremes, Cousens painted 'a number of scenarios, where we see a less dramatic year-upon-year increase. In one case, it's about 1,600."

"These alternatives," he continued, "illustrate that even in several years' time, the message of the *Nature* paper, in response to that question, is: No, we can't rule out the possibility of a large epidemic."

He observed: "At the present time there is enormous uncertainty, which makes people very uncomfortable. But I'm afraid it's what the message is." ■

Claims

19. Bovine growth hormone produced by a method which comprises culturing cells which contain a recombinant DNA molecule which DNA molecule comprises a nucleotide sequence encoding bovine growth hormone comprising the amino acid sequence at positions 2-191 of Figure 1 or an allelic variant thereof, said encoding nucleotide sequence contained in an expression system effective in producing said encoded bovine growth hormone in a recombinant host cell,

said culturing under conditions wherein the encoding nucleotide sequence is expressed to produce said bovine growth hormone; and

recovering the bovine growth hormone from the culture.

20. The bovine growth hormone of claim 19 which comprises the amino acid sequence at positions 2-191 of Figure 1.

21. The bovine growth hormone of claim 19 wherein the cells are *E. coli*.

22. The bovine growth hormone of claim 19 which is in purified and isolated form.